

Chapter 10. Overt Mental Illnesses

Major Points

- **People with mental illness may simply have more extreme Big Three strengths than normal people; in addition, mental illness may exist with normal Big Three strengths but these transmitter systems have become dysfunctional.**
- **Clonidine and the other alpha 2 adrenergic agonist drugs may be superior to lithium, the anticonvulsants, and the atypical antipsychotics for the treatment of bipolar disorder.**
- **Prozac and the other ser reuptake inhibitor (SRI) drugs may be superior to both the typical and the atypical antipsychotics for the treatment of schizophrenia.**
- **Drug and alcohol abuse is a sign of low quality of life that may be treatable with The Adjustment.**

In my opinion people with overt mental illnesses, that is, *DSM-IV-TR* diagnosable mental illnesses, are just more extreme Big Three variants than so called normal people. In particular, the greater a person's ser and nore strengths deviate from mid-range values, the closer that person is to having an overt mental illness, or if he suffers from a mental illness the more intense that illness is. Therefore, mental health treatment should focus upon performing The Adjustment, by adjusting ser and nore strengths with Big Three drugs closer to mid-range, optimal degrees. In addition, overt mental illness may exist with normal ser and nore strengths, but one or both of these transmitter systems has become dysfunctional and the circuitry needs to be reset with a Big Three drug or ECT, or instead non-optimal strengths and dysfunction may coexist in a given person.

Since overt mental illnesses blend into one another among different people, and drug treatments do so as well, isn't this consistent with an underlying Big Three mechanism for both? Drug based Big Three alterations such as The Adjustment may be *indirect* treatments of overt mental illnesses, but they generally are effective. Just because drug adjustment of the Big Three circuits can treat a given mental illness does not mean that illness was caused by an equal and opposite disturbance of the Big Three—these transmitters could just be inputs to other brain circuits, ways of perturbing circuits. That said, I do believe that disturbance of the Big Three systems really does *cause* at least most types of mental illness.

When, if ever, is irreversible damage done to the brain by mental illness? In the book *Against Depression*, Peter Kramer discusses evidence for damage to the brain caused by depression. Moreover, some cases of schizophrenia appear to be associated with brain atrophy. So what role, if any, does neuron death or birth play in mental illness?

Do many people have a ser deficiency, as Michael Norden has suggested in *Beyond Prozac*? Is it healthy to have as much ser as possible, or is too much of it unhealthy, as the current theory would suggest? A prevailing view is that many people are deficient in ser, but perhaps this is not the case, though I think many people have

personality traits of weak ser (see Chapter 12). Another common view is that the more ser one has, the happier one is, though I don't believe that this is the case.

Many mental illnesses can be episodic in that they flare up from time to time—this is well established for unipolar depression, bipolar disorder, and schizophrenia. Are all mental illnesses actually episodic, or at least not constant over time?

Maybe the brain repels overt mental illnesses—induced by stress or other, possibly natural stimuli—all the time, and only in a few cases, perhaps in susceptible individuals, do we see it break through. Perhaps there are many near misses.

In reading about the specific mental illnesses below, the reader will notice that the most common Big Three strength combination in these illnesses is weak ser and/or strong nore, which is a recurring theme in this book. According to the The Adjustment theory, people with this pair of strengths would best be treated by using two drugs simultaneously: one drug that strengthens weak ser and another drug that weakens strong nore. Other people will only need one drug, because only ser is weak or nore is strong. See Chapters 8 and 9 for details on which drugs to use and how to use them in this manner, as well as for treating other combinations of pathological Big Three strengths.

Depression

Causes and Treatments

Depression may be caused by non-optimal strengths of ser and/or nore, the dysfunction of ser/nore circuits, or both of these phenomena. If dysfunction is necessary for depression, then non-optimal ser and/or nore strengths can also contribute by making the depression more intense. Indeed, strong ser and nore should be just as pathological as weak ser and nore in exacerbating depression, even though psychiatrists typically only use ser and/or nore strengthening antidepressants to treat it. Recall that the ser weakening drug tianeptine treats depression, and the antidepressant effect of the atypical antipsychotics may also be mediated by ser weakening. So resetting of ser/nore circuitry—in most cases through a level change—may be the universal feature of antidepressants and ECT. For these reasons, I think of lack of depression as a logical AND (introduced in Chapter 6) for the ser and nore systems, where both systems must be functional and at mid-range, optimal strengths to produce optimal mood.

So are there ser or nore specific depressions? Possibly. And how does OR circuit modulation relate to this? OR logic implies that any drug that optimizes (or at least strengthens or weakens) ser or nore will reset the depression circuits and treat the illness—however, this is argued against by a study that shows ser strengthening without an antidepressant effect in some depressed persons. OR also implies that a ser drug or a nore drug should both work in the same person, and is argued for by the fact that SRIs and NRIs each work in about 70% of depressed people—with these percentages many people should respond well to either class of drugs. This sort of reasoning in favor of OR leads to the conclusion that practically any ser and/or nore drug can treat depression, including the typical antipsychotics (if they all indeed weaken ser), the alpha 2 adrenergic agonists such as clonidine, and the 5HT_{2A} receptor deactivators such as cyproheptadine. So while I acknowledge that treating depression as a logical OR for ser and nore drug manipulations is promising and deserves more scientific attention, I still

think that ser AND nore must be at mid-range, non-dysfunctional strengths for optimal mood, and this must be considered during drug treatment.

Though we may use a simple ser AND nore drug treatment strategy for attacking all depressions, there may still be different types of depressions, with different underlying Big Three neurotransmitter system abnormalities, that require different drug regimens in order to render ser AND nore at optimal, mid-range strengths. If so, maybe these depressions can be distinguished in terms of their effects on sleep, appetite, and diurnal (within the day) fluctuation in mood. One well known subtype of depression is atypical depression, which is characterized by: oversleeping and overeating, mood brightening transiently in response to positive external events, sensitivity to interpersonal rejection, and heavy, leaden feelings in the arms and legs. Perhaps in the majority of cases atypical depression involves weak ser (and strong nore), since it has been shown to respond better to SRIs than to NRIs. However, if strong nore is part of the pathology, NRIs should actually make the depression *worse*, and nore weakening drugs such as clonidine should treat it. A further test of atypical depression involving strong nore is whether such people have personality traits of strong nore.

Two other potential subtypes of depression that are very likely an oversimplification: undersleeping signifies severe depression, and oversleeping signifies mild or moderate depression. My Case Study is an example that the same person can oversleep and undersleep at different times during the course of treatment for depression, though I underslept during my most severe depression and overslept during milder depression.

Another potential subtype of depression is psychotic depression, during which the individual experiences hallucinations and/or delusions, as well as a depressed mood. Psychotic depression may respond better to SRIs than to NRIs, similar to atypical depression, since psychosis may be caused by weak or dysfunctional ser, or a low ser/nore strength ratio, consistent with my proposed mechanism of the hallucinogen, LSD (see Chapter 9), which itself causes psychosis. Moreover, if psychosis is caused by a low ser/nore ratio, then NRIs should make psychotic depression worse.

Most people with depression feel better as the day wears on, though some feel worse, and these are two other potential subtypes of depression. Keep in mind that since, as described in Chapter 4, ser and nore build as the day wears on, depressions that get better or worse as the day wears on may have something to do with this putative transmitter build-up. I think depressions that get worse as the day wears on are due to build-up of nore, and should respond to nore weakening and/or ser strengthening drugs and not the opposite adjustments.

Whether a particular person's depression lowers self-esteem may be a clue to the underlying Big Three abnormality, since ser (and dop) strength partially encode self-esteem (see Chapter 7).

Can everyone become depressed with a great enough stressor? Possibly, though perhaps expanded dysthymics (discussed in the next chapter), who suffer from constant mild depression, are more likely to be affected. The continuum theory for depression, namely that the less optimal a person's strengths of ser and nore, the greater the severity of her depression, is consistent with the hypothesis that some people are 'farther away from depression' than others if their Big Three systems are better optimized. And maybe depression is more common in dysthymics if mild depression is more likely to set off a

snowballing effect involving escalating responses to stressors that eventually results in more severe depression.

Relationship to Stress

Stress is thought to be a cause of depression—and other types of mental illness—in at least some cases. A possible mechanism is that stress causes a massive release of the Big Three from their brainstem neurons, followed by a diminished release of these transmitters, leading to subsequent dysfunction and/or abnormally low strengths of the Big Three, especially ser and/or nore. However, summary data from the book, *Manic-Depressive Illness*, suggest that lower levels of the Big Three during depression may only be the case for dop. But, if depression is *totally* caused by weak dop, then cocaine, Ritalin, and amphetamine should totally reverse it, at least temporarily, but they do not.

Speaking of stress, which aspects of American society contribute to causing depression by increasing stress on the individual? Theory: 1) non-nomadic living conditions, 2) isolated living conditions, 3) isolated working conditions, 4) unnaturally stressful work itself, and 5) availability of too much information.

Two Week Delay

Finally, the two week delay in response to antidepressants—and many other Big Three drugs—is one of the principal reasons researchers have strayed from the Big Three/biogenic amine *level* hypothesis of depression, but this delay can easily be explained by the internal regulation of the postsynaptic circuitry, where a safety factor in the pathway renders the circuit unresponsive to an immediate boosting of ser and/or nore (see Chapter 4 for more details).

Bipolar Disorder

Typical and Atypical

Psychiatry already recognizes at least two subtypes of bipolar disorder: bipolar I and bipolar II, which involve episodes of full-blown mania (bipolar I) and mild mania (hypomania; bipolar II), interspersed with episodes of depression. So bipolar I is the more severe of the two subtypes. I think there are at least two other subtypes of bipolar disorder—typical and atypical—that may each contain individuals with bipolar I and bipolar II. I refer to typical bipolar disorder as ‘typical’ because it is by far the most common of the two subtypes—perhaps 100 times more common than atypical bipolar disorder, based on the personality characteristics of bipolar persons I have known or known about. Typical bipolar disorder is characterized by genetically strong nore and weak ser, whereas atypical bipolar disorder is characterized by genetically strong ser and weak nore. The existence of typical and atypical bipolar disorder follows directly from The Triangle (see Chapter 5), since genetically strong ser or strong nore tends to produce the strong dop that is characteristic of mania/hypomania.

In addition to the standard manic symptoms listed in the *DSM-IV-TR*, typical (strong nore, strong dop) mania may be distinguished from atypical (strong ser, strong dop) mania in that typical mania may produce: decreased need for sleep, presence of

hallucinations and/or delusions, heightening of the five senses, and decreased sensitivity to the cold. In contrast, atypical mania (as in My Case Study) may produce: decreased sleep (without feeling rested), absence of hallucinations and delusions, deadening of the five senses, and increased sensitivity to the cold. Both types of mania may result in reduced emotional sensitivity, and strengthened dop may be the cause of this insensitivity. If ser and dop encode self-esteem, then the atypical bipolars/hypomanics may have the highest self-esteem of anyone, though typical bipolars/hypomanics may also have high self-esteem due to strong dop.

So the cause of typical mania/hypomania is that the strength of nore has increased—possibly due to an environmental trigger such as stress, and always accompanied by strong genetic nore—causing the dop strength to also increase (as in The Triangle), and it is this elevated dop strength that causes most of the symptoms. (Recall that cocaine, a dop strengthener, produces a high that is similar to that in mania.) As the nore and dop strengths increase, they weaken ser (also described in The Triangle), and it is this weakened ser (or low ser/nore ratio) that causes the hallucinations and delusions present in typical mania.

Atypical mania/hypomania (as in My Case Study) is similar except it involves strong ser instead of strong nore. It is possible that atypical mania can only be induced in people by ser strengthening drugs such as the SRIs, since very strong genetic ser is so rare, whereas typical mania can have either external (such as drugs or seasons) or internal (such as genetics) causes. Atypical antipsychotics, which directly weaken ser and dop, are ideal for treating atypical mania, though they can also treat the strong dop aspect of typical mania.

Both subtypes of bipolar disorder seem to involve pathological imbalances of ser and nore, in which one is strong and the other is weak, based on the personality characteristics of bipolar persons I have known or known about. And the greater the imbalance of ser and nore, the greater the pathology, which follows from The Adjustment theory itself. Therefore, if nearly all or all bipolar people (and many people who are hypomanic all the time) have a pathological ser/nore imbalance, then use of a drug such as an antidepressant that strengthens the weak one as well as a drug that weakens the strong one should be standard treatment (as in My Case Study), though adding antidepressants in bipolar treatment remains controversial because many of these drugs can trigger mania or rapid mood cycling.

Furthermore, due to this putative ser/nore imbalance that may exist whether the person's mood is cycling or is not (due to a mood stabilizing drug), perhaps a lot of bipolar persons are non-compliant with their medication, in that they stop taking their medication without approval from their doctor, not only because they miss being hypomanic—if they indeed have stopped cycling—but also because their quality of life is lower than a 'normal' person's quality of life. Such poorer quality of life—a type of expanded dysthymia, discussed in the next chapter—may be the case even though psychiatrists may tell the person that life on medication is what it's like to be normal, when in fact they are not on the proper regimen of medication at all: a proper regimen would involve performing The Adjustment. So maybe for bipolar II disorder (in which the person is continuously cycling), mild cycling may be a better treatment option than total stoppage of cycling—if total stoppage is even possible—since the person may crave hypomania and be non-compliant without it.

As stated in Chapter 9, perhaps clonidine and the other alpha 2 adrenergic agonists only weaken nore in the short term and not in the long term due to drug adaptation by the brain. But if these drugs do indeed weaken nore in the long term—and I think they do—they could be landmark drugs for (typical) bipolar disorder (especially when used in conjunction with a ser strengthening drug). Indeed, the alpha 2 agonists may be superior mood stabilizers, in their overall effect on quality of life, than lithium, the anticonvulsants, the atypical antipsychotics, and the typical antipsychotics, particularly if lithium and the anticonvulsants don't weaken nore.

Bipolar I and Bipolar II

Bipolar I and bipolar II are the two well-established subtypes of bipolar disorder, where bipolar I is characterized by full-blown episodes of mania and bipolar II has episodes of hypomania. These two subtypes may in fact be related to one another as a continuum among different people, just as mania to hypomania or atypical to typical bipolar disorder may be continua, though if bipolar I and bipolar II have different seasonal patterns—which they probably don't in all cases—they may really represent two categories.

Do people with bipolar I or bipolar II disorder ever really stop mood cycling? The conventional wisdom is that people with bipolar I have normal moods between manias and depressions and people with bipolar II don't.

It would be consistent with the so-called permissive hypothesis of mania, which states that weak genetic ser 'permits' induction of full-blown mania in people with bipolar disorder, if bipolar II people tend to have stronger ser than bipolar I people, since those with bipolar I have full-blown episodes of mania. However, the permissive hypothesis probably isn't true, just based on the personality traits of bipolars I've known who had very weak ser without full-blown mania, making them bipolar II and not bipolar I. Moreover, the permissive hypothesis is argued against by the general finding that SRIs induce mania in bipolars. A variant of the permissive hypothesis that may be true: genetically weak ser is necessary but not sufficient for full-blown mania.

One clear principle in the drug treatment of all subtypes of bipolar disorder is that they should either be treated with a mood stabilizer, or a mood stabilizer and an antidepressant, but never with an antidepressant alone, since an antidepressant alone will induce mania and/or rapid, pathological mood cycling. So does increasing the dose of standard mood stabilizer, such as lithium and the anticonvulsants, turn bipolar I into bipolar II in a given person? And does increasing the dose of an antidepressant do the opposite? In both cases: probably not, as if there are hardwired, largely genetic brain differences between the two bipolar subtypes. For treating bipolar depression, especially bipolar II depression, one may never need to use a higher dose of an antidepressant (in conjunction with a mood stabilizer, of course) than that which makes one hypomanic. Higher doses may produce pathological, rapid mood cycling (as in My Case Study).

Brain Mechanisms

Big Three drugs—and lithium and the anticonvulsants, possibly—affect the frequency (how often it occurs) and amplitude (how severe it is) of bipolar disorder mood cycling, as well as other perceptual phenomena, such as how sharp one's five senses are,

associated with depression and mania. In My Case Study, strengthening weak nore and weakening strong ser (i.e., The Adjustment) made my hypomanias more enjoyable and my depressions less pathological.

For people with bipolar disorder, an episode of mania or hypomania is usually followed by a crash into depression, and then the cycle repeats. So bipolar disorder may involve a 'switch in the brain' for shutting off mania/hypomania and turning on depression, a function which every brain has but in most individuals is never invoked because they never get—or are incapable of getting—manic or hypomanic. The switch may have different thresholds in different people, explaining the existence of constant hypomanics. In other words, people who are constantly hypomanic may have a high threshold for their switch, such that they remain hypomanic all the time. Likewise, there may be a switch for shutting off depression and turning on mania/hypomania.

In My Case Study, the transition from hypomania to depression was sometimes instantaneous, though for most people gradual transitions are probably the norm. Nonetheless, what does *instantaneous* switching tell one about Big Three strengths changing as the putative switching mechanism? This may rule out Big Three brain extracellular level changing—which should be relatively slow—as the mechanism. Similarly, do the Big Three 'push a swinging gate' in the brain circuitry, that flips from on (mania) to off (depression) with potentially rapid, or even instantaneous, transitions between the two states, or is there no such gate in bipolar disorder? What does immediate termination of mania by dop weakeners tell one about this? And if bipolar disorder involves multiple brain circuits—in other words, multiple parallel processes—these circuits may have different rates at which they cycle, such that they are not synchronous. For example, at a given time, the circuits that control sensory sharpness may be affected differently than the circuits that control the subject matter of thought.

If mania involves strong ser or nore—as well as strong dop—can it really be terminated immediately by just a dop weakener? Apparently it can be. Moreover, is the mechanism of terminating mania different for lithium, the anticonvulsants, and the antipsychotics? If it is, this is a clue regarding the mechanisms underlying mania and the mechanisms of these drugs.

Ultra-rapid cycling bipolar disorder, in which mood—or at least emotion—fluctuates dramatically within a single day, may be caused by super strong nore, or a high nore/ser ratio, possibly interacting with particular hardwired circuits. In other words, if strong nore plays an important role in producing emotions (see Chapter 7), weakening nore may result in a type of mood stabilization, independent of and confused with stabilizing standard bipolar disorder.

Perhaps the default for some bipolar people is to *always* get manic when taking no drugs—though this may be subsequently followed by depression—whereas the default for others is to *always* get depressed when taking no drugs, as in My Case Study. Perhaps this is an important distinction that requires different approaches to drug treatment. In other words, the always manic type may not require an antidepressant but only a mood stabilizer, whereas the always depressed type may require both an antidepressant and a mood stabilizer.

In mood cycling we must distinguish between internal causes (produced by a combination of genetics and past experience) and external causes (such as the seasons, drugs, stress, possibly other recent environmental conditions such as sleep deprivation).

Along these lines, to what extent can the individual affect the cycling of his own mood? In particular, can the individual push himself for a number of days and then cause a subsequent depression? It should be noted that sleep deprivation can induce mania, and a person can, to some extent, also regulate exposure to stress.

What does it mean that even tiny doses of antidepressants induce mania/hypomania in bipolar individuals, even, as in My Case Study, for a stress induced depression? It is as if the antidepressant is working on a stage in the cortical circuitry that is different from the one that the stress altered, or is just resetting the circuitry.

Additional Observations

Why is bipolar disorder a predictor of wealth? (Note: for a discussion of this subject, see Goodwin and Jamison's *Manic-Depressive Illness*.) For example, since most bipolar persons have both periods of depression and periods of mania, and if these ups and downs balance each other out, a bipolar person should be average—in terms of productivity, income, etc.—yet often they are not. This implies that even while depressed (or in a mixed mood), many bipolar people have above average energy (and/or possibly above average intellect). On the other hand, many bipolar individuals are occupationally impaired due to their disorder.

What does the genetic relatedness of bipolar disorder and unipolar depression (i.e., a mental illness in which people only have depression) mean with respect to the Big Three (aka, biogenic amine or chemical imbalance) theory of depression and mania, particularly with regard to the genetic strengths of the Big Three? Indeed, the offspring/relatives of unipolar depressives not only have elevated rates of unipolar depression but also have elevated rates of bipolar disorder, and the offspring/relatives of bipolars not only have elevated rates of bipolar disorder but also elevated rates of unipolar depression. The biogenic amine theory would predict that the two illnesses be *anticorrelated* among different relatives, since low levels of the Big Three should produce depression and high levels should produce mania. In other words, the biogenic amine theory would predict that the offspring/relatives of unipolar depressives have very low rates of bipolar disorder (and vice versa), due to the inheritance of genes encoding low levels of the Big Three. However, this may not be the case if there is often an underlying imbalance of ser and nore—one strong and the other weak—in both bipolar disorder and unipolar depression. If typical bipolar disorder involves strong nore and so does atypical depression, do depressed relatives of typical bipolars show atypical depressive features? Finally, if bipolar disorder really has a nearly 100% concordance rate between identical twins, which means that when one twin has the disorder, the other twin nearly always does as well, as has been reported, then perhaps it isn't usually brought on by unusual stress, though it may be exacerbated by stress.

Seasonal Affective Disorder (SAD)

SAD is a common disorder that is characterized by seasonal changes in mood, in most cases by wintertime depression. The relationship between SAD and bipolar disorder is unclear, as bipolar disorder also in many cases has a seasonal pattern, often with wintertime depression. There may be partial overlap in the occurrence of SAD and

bipolar disorder among different people, and if so this would be another example of mental illnesses blending together. It would be interesting if *all* bipolar disorders turn out to be seasonal—or at least have a seasonal component or shift in the average degree of depression or mania. Alternatively, SAD may be a special type of bipolar disorder. And perhaps other mental illnesses, particularly unipolar depression, have a seasonal component.

If the cause of wintertime depression in SAD is mediated by seasonal changes in light, is it mediated by: the total amount of light exposure over many days, just the peak intensity of light delivered for a very short amount of time each day, the rate of change of the length of day as the seasons change, or the absolute length of daylight in different seasons? All are obvious points that researchers of SAD have probably considered. However, My Case Study indicates that bright light therapy, which is the standard treatment of SAD, does not necessarily reverse wintertime depression, but instead simply strengthens ser. Therefore, the cause of wintertime depression may not involve light at all, but rather some other external (such as temperature) or internal (such as a biological clock, analogous to a circadian rhythm) signal. Moreover, bright light therapy may strengthen ser in everyone, not just those with SAD, and may be effective in all seasons—which would be a landmark discovery for the treatment of mental illness, especially depression. In other words, bright light therapy may not be producing an effect that is equal and opposite to the cause of seasonal depression—it may have an antidepressant effect with a different, independent mechanism of action, such as ser strengthening. One study indicates that personality changes associated with bright light therapy are consistent with ser strengthening.

According to another study, bright light therapy for SAD does not boost Big Three transmitter *levels*, indicative of an antidepressant effect independent of level boosting, which might represent a separate brain mechanism that could be capitalized upon by new types of antidepressant drugs. But even if the ser level isn't boosted, the ser circuitry could still be strengthened. And evidence from My Case Study is consistent with ser level boosting: bright light therapy upset my gut, made my hands cold and shaky, and produced a state of hypomania similar to that induced by Zoloft.

Another possible treatment for SAD is dawn simulation via a light in the bedroom that gradually gets brighter as dawn approaches. One study indicates that dawn simulation is superior to bright light therapy in treating wintertime depression. As in bright light therapy for SAD, the variables of dawn simulation may be critical: time of morning, duration of light exposure each day, light spectrum, and light intensity.

If SAD was selected for by evolution to regulate seasonal behavior, and may be critical to the survival and reproduction of the individual, then maybe it is produced by a combination of several brain mechanisms, since a single brain mechanism may be less reliable. These mechanisms could include more than one of: an internal clock, temperature change, light change, or any other physiologically detectible seasonal difference. The less common, and the less essential for survival and reproduction the SAD, the less likely that it is mediated by several mechanisms, and the more likely it would be responsive to a single type of treatment such as bright light therapy.

Here's a possible experiment that would provide clues to the brain mechanism of SAD: what happens when someone with wintertime depression moves from the northern hemisphere to the southern hemisphere, or vice versa, since the timing of the seasons

reverses? Does his depression shift to the new wintertime? If SAD is based on an internal clock then there may be no shift of seasons, but if SAD really is based on external wintertime cues then it should shift.

If the SAD mechanism turns out to be a ser or nore level change (and maybe even if it is instead a strength change elsewhere in the ser/nore brain circuitry), it can probably be compensated for by increasing the dose of antidepressant during the wintertime—or in the summertime, in the case of SAD with summertime depression. However, flux due to changes in types of drugs and/or their dosages (see Chapter 9) may make seasonal changes in their use decrease rather than increase quality of life.

Finally, people diagnosed with SAD, who are responsive to bright light therapy, may actually represent at least two categories of patients: those who are very sensitive to ambient lighting throughout the year and have a lower mood during the wintertime since there is less sunlight, and those who are not sensitive to ambient lighting (as in My Case Study) but nonetheless have a decrease in average mood during the wintertime. The first category of patients may be immediate responders to bright light therapy, whereas patients in the second category may take a week or more of bright light therapy before experiencing an improvement in mood (a timecourse that is similar to taking an antidepressant drug).

Schizophrenia

Causes and Treatments

Since the advent of antipsychotic drug treatment in the 1950s, it has been widely hypothesized that schizophrenia is caused by strong dop, since dop weakening antipsychotic drugs terminate its psychosis. However, a recent study has shown that typical antipsychotics, such as Haldol and Thorazine, directly weaken ser as well as dop, as do the atypical antipsychotics, such as Zyprexa and Geodon, so the actual neural basis of schizophrenia may be based in ser rather than dop. And even though therapeutic response (how much better the patient gets) to typical antipsychotics correlates with how well these drugs bind to the dop D2 receptor, maybe therapeutic response also correlates with how well they bind to the ser 5HT_{2A} receptor, which I think is the principal ser receptor involved in mental illness. In addition, according to The Triangle (see Chapter 5), dop weakens ser, so perhaps when antipsychotics weaken dop this strengthens ser, thereby strengthening weak ser and/or resetting dysfunctional ser circuitry.

Here are some more arguments against schizophrenia being caused by strong dop (where traits 2–5 would be mediated by strong dop): 1) dop neurons do not send connections as strongly to sensory cortex (which should be involved in hallucinations) as they do to prefrontal cortex; 2) schizophrenics don't have dominant traits, and bipolars do—measured in wealth alone, though there are many exceptions; 3) they don't have racing thoughts—in fact, they tend to have poverty (i.e., diminishment) of thought or derailment (i.e., wandering) of thought, consistent with hypofrontality; 4) they don't have stimulus seeking traits; 5) they don't have high energy or exhibit hyperactivity; and 6) antipsychotic drugs terminate psychosis after weeks, not minutes, even though dop weakening occurs in minutes and there is no dop safety factor.

The current theory hypothesizes that schizophrenia is actually caused by weak and/or dysfunctional ser rather than strong dop (or strong ser), for the reasons listed above and since: 1) the street drug LSD, which may weaken ser (see Chapter 9), produces hallucinations, delusions, paranoia, catatonia (paralysis of movement), insomnia, and derailment of thought; 2) ser is distributed throughout the thinking (prefrontal) and sensory regions of the brain, whereas dop is more concentrated just in the thinking region of the brain. If schizophrenia is indeed caused by weak ser, then SRIs such as Prozac should treat both its positive symptoms (such as hallucinations, delusions, and disorganized speech) and its negative symptoms (such as lingering apathy, emotional flattening, and poverty of speech), and this would be a landmark discovery and improvement in treatment. Moreover, the negative symptoms are consistent with expanded dysthymia (discussed in the next chapter) due to weak ser. Derailment of thought and disorganized thought or speech may be due to lack of a ser filter for filtering out irrelevant details. Consistent with weak or dysfunctional ser causing schizophrenia, a genetics study has revealed a chromosomal region associated with susceptibility “not only for schizophrenia but also for anxiety-related personality traits such as harm avoidance and neuroticism”. Moreover, alleles (variants of a gene) of the 5HT_{2A} receptor have been directly associated with schizophrenia. Schizophrenics can also exhibit autistic symptoms, sharpened senses, and enhanced musical ability, as described in Sol Snyder’s classic book, *Madness and the Brain*—all consistent with weak ser (and in the latter two of these traits, consistent with strong nore). Schizophrenia often coexists with obsessive-compulsive disorder (OCD), and OCD is often treatable with SRIs. Finally, the schizophrenics I’ve met have the personality characteristics of weak ser, not strong ser or strong dop, though some have strong nore characteristics as well.

LSD psychosis mimics schizophrenia far better than cocaine or amphetamine psychosis, or ketamine or PCP (‘angel dust’) psychosis, where these latter four drugs are often thought to produce stuporous states that resemble schizophrenia. Cocaine or amphetamine psychosis is a poor model of schizophrenia for several reasons, since these drugs: 1) produce hyperactivity rather than catatonia; 2) produce euphoria rather than apathy or depression; 3) produce racing, related thoughts rather than derailment and poverty of thought; 4) produce excessive speech rather than poverty of speech; and 5) produce a much less delusional state than schizophrenia. However, it’s possible that *long-term* use of cocaine or amphetamine can induce a state of psychosis that is more similar to that in schizophrenia. In addition, NMDA receptor (which is a brain receptor for the neurotransmitter glutamate) binding drugs, such as ketamine and PCP, are also poor models of schizophrenia, although these drugs can produce a stuporous state resembling catatonia, though so can LSD.

An alternative to the strong dop and weak ser hypotheses is that schizophrenia is produced by strong nore. If so, schizophrenia, like typical bipolar disorder, should be more prevalent among artists—who I hypothesize to be strong in nore (see Chapter 12)—than among the general population. I think strong nore is the distant second best explanation for schizophrenia after weak or dysfunctional ser, mainly because of LSD, which seems to be specific to ser. Moreover, the effectiveness of dop weakening antipsychotics in treating schizophrenia may also be inconsistent with schizophrenia being caused by strong nore, since due to The Triangle weakening dop should *strengthen* nore and make the psychosis worse. Nonetheless, weak ser producing psychosis may be a

special case of a low ser/nore ratio producing psychosis. If schizophrenia is indeed produced by a low ser/nore ratio, then the most effective treatment, according to The Adjustment, is to strengthen ser with an SRI drug such as Prozac, and simultaneously weaken nore with an alpha 2 adrenergic agonist drug such as clonidine.

A possible experiment: add an SRI, an NRI, or Ritalin (a dop strengthener) to the standard antipsychotic regimen of schizophrenics. How do these Big Three manipulations affect the positive or negative symptoms of the illness? Next experiment: compare an SRI to tianeptine or cyproheptadine, which are ser weakeners. Tianeptine and cyproheptadine could, like an SRI, reset dysfunctional ser circuits, though I think the SRIs should produce an overall superior effect. As mentioned above, if schizophrenia is affected by nore, alpha 2 adrenergic agonists such as clonidine should affect its outcome, and preliminary data support this hypothesis. Moreover, preliminary data indicate that the nore weakening beta blocker propranolol may have some efficacy in treating schizophrenia.

Brain structural abnormalities, such as general atrophy, that have been associated with some cases of schizophrenia may be caused by long-term Big Three abnormalities, or long-term consequences of the illness itself.

Comparison with Other Psychotic States

On a more general note, are there systematic differences in the psychosis between schizophrenia, typical mania, and psychotic depression, even if all three illnesses are at least partially caused by weak or dysfunctional ser? For example, are the characteristics of paranoia or hallucinations different in these three illnesses, as this may provide evidence as to whether they have a common cause? Perhaps a similar Big Three drug treatment, such as the SRIs or tianeptine, can be used for all three illnesses. And if schizophrenia drugs, such as the atypical antipsychotics, can treat mania, can mania drugs (lithium, anticonvulsants) treat schizophrenia?

I'm not suggesting that schizophrenia should no longer be treated with the standard antipsychotic drugs, but rather that ser resetting or strengthening may be the actual basis of such treatment, and that further research should be conducted to test this hypothesis. So it's possible that the SRIs are the best available drugs for treating schizophrenia, both for treating its positive and its negative symptoms, and this would be a landmark breakthrough for the treatment of this illness (especially considering that treatment of the illness with existing antipsychotic drugs is often not very effective). There's already ample evidence that the SRIs can treat its negative symptoms, which may be due to weak ser as well as weak dop, and there's preliminary evidence that these drugs can treat its positive symptoms as well.

Attention Deficit Hyperactivity Disorder (ADHD)

The current theory puts forth two alternative hypotheses for the cause of ADHD: 1) prefrontal hypofrontality (i.e., poor functioning of this part of the brain) due to weak dop, where according to The Triangle (see Chapter 5), weak dop may be caused by weak ser and/or weak nore; 2) sensory-emotional hypersensitivity due to weak ser and perhaps strong nore. I think 1) is the more credible hypothesis, partly because hypofrontality may

explain the characteristic hyperactivity due to lack of planning of movement, since the prefrontal cortex is involved in such planning. In other words, people with ADHD may be reacting immediately to nearly every incoming stimulus in their environment or their thoughts, instead of having more calculated, selective reactions to these stimuli based on a consistent plan of action. In ADHD individuals, cocaine and amphetamines, which are dop strengtheners, cause focus, not euphoria, consistent with these people having hypofrontality. In other words, these drugs restore normal functioning to prefrontal cortex in people with ADHD, though I'm not suggesting that people with ADHD should use cocaine. A possible experiment: give ADHD individuals: 1) an SRI, 2) an NRI, 3) Ritalin (a dop strengthener), 4) both an SRI and an NRI, and see which treatment is best.

In *Shadow Syndromes*, Ratey and Johnson point out that people with ADHD can be quite successful, always seeking the next stimulus. Stimulus seeking behavior may also be related to strong dop according to Cloninger (see Chapter 12); so whether weak or strong, dop may be implicated in stimulus seeking. As we'll discuss in Chapter 13, dop can also affect dominance, so what is the relationship between ADHD, hypofrontality, and dominance? Even though I hypothesize that dop is usually strong in dominant individuals, the stimulus seeking aspects of ADHD may also produce dominant characteristics. Nonetheless, at least some aspects of cognition are impaired in ADHD, and this may diminish dominance.

ADHD can be confused with or coexist with depression—another example of mental illnesses blending into one another—and it may also be confused with bipolar disorder, since mania/hypomania due to bipolar disorder may mimic some of the symptoms of ADHD, such as inability to concentrate and hyperactivity. ADHD also blends into Tourette's syndrome, where both illnesses are characterized by impulsiveness. Obsessive-compulsive disorder (OCD) also appears to blend with both illnesses, and clonidine (a nore weakener) is a standard treatment for Tourette's.

Anxiety

Anxiety is a feeling of which we are consciously aware, and anxiety disorders probably evolved, like other mental illnesses, to drive behavior in various ways. It is not surprising that anxiety often occurs in people with weak ser (and possibly strong nore), since some weak ser people may fulfill a personality niche associated with hypervigilance, including having acute senses. In other words, such people are constantly scanning the environment for signs of danger, and this may have aided in their survival during the course of evolution. It is less clear to me why anxiety often coexists with depression, though an overlap in brain circuitry may be involved. If some people are incredibly anxious, maybe some people are pathologically calm, as in people with super strong ser and/or super weak nore.

We can classify the overt anxiety disorders as either long-standing or transient. Both genetically weak ser and strong nore may play a role in these disorders, though the role of weak ser may be more important. So the most effective treatment for them all, according to *The Adjustment*, is to strengthen ser with an SRI drug such as Prozac, and simultaneously weaken nore with an alpha 2 adrenergic agonist drug such as clonidine.

Long-standing anxiety disorders: agoraphobia, specific phobias, social phobia, generalized anxiety disorder, and obsessive-compulsive disorder (OCD). In most cases, the disorder has been present for nearly all of the individual's life, or at least nearly all of their adult life.

Transient anxiety disorders: panic attacks, panic disorder, post-traumatic stress disorder, and acute stress disorder. Principal cause: genetically weak ser that has been made weaker and/or dysfunctional by environmental stress, and possibly strong and/or dysfunctional nore. In most cases, the disorder has only been present since the stressful event.

Alpha 2 adrenergic antagonists (such as yohimbine and idazoxan), which probably strengthen nore, increase anxiety and arousal, whereas alpha 2 adrenergic agonists such as clonidine, which probably weaken nore, can reduce anxiety and arousal. Neither class of drugs is currently widely used for psychiatric purposes in the United States. In addition, the nore weakening beta blocker propranolol has been shown to decrease anxiety in preliminary studies.

Generalized anxiety disorder may be caused by weak ser and/or strong nore, consistent with sensory-emotional hypersensitivity (see Chapter 7). It may be paradoxical that individuals with weak ser and strong nore are in many cases anxious, because of the role of strong nore in some cases of dominance (see Chapter 13).

SRI, NRI, and MAOI—the latter of which probably strengthen ser and nore—all treat panic attacks (but in the same person?). This is paradoxical if nore strengthening drugs such as the NRIs can also increase general anxiety—perhaps panic attacks and general anxiety are mediated by different Big Three circuits. Likewise, propranolol and clonidine, putative nore weakeners, also treat panic attacks. Maybe resetting of dysfunctional nore is the mechanism for all of these nore drugs in treating such attacks. So both ser and nore may be involved in panic attacks—an AND in the ser/nore circuits, in that both systems have to be intact in order to be free of the attacks.

Anxiety also appears to be quelled by dop. Cigarette smoking, which strengthens dop, tends to quell anxiety. Also the drug Zyban, which may strengthen dop and is chemically identical to Wellbutrin, is effective in helping people quit smoking.

Historically, two classes of drugs—the barbiturates and the benzodiazepines (such as Valium, Klonopin, and Xanax)—have been the standard treatments for general anxiety, and both classes of drugs bind to GABA receptors in the brain. GABA is the brain's principal inhibitory neurotransmitter, and by binding to GABA receptors these drugs quell neural activity throughout the brain in a very general manner. I believe that affecting GABA receptors is an indirect treatment of anxiety, which is caused by weak ser and/or strong nore, and should ideally be treated with ser and nore drugs. In contrast, the barbiturates and benzodiazepines provide a poorer treatment, since they are addictive, require increasingly higher doses to maintain their effect, and produce a 'drugged' feeling.

Drug and Alcohol Abuse

Psychologists have long recognized that a particular pattern of behavior, such as alcohol abuse, is likely to become a habit if that behavior produces an overall positive experience in the individual. This implies that a mentally healthy, happy person could, if the stimulus is positive enough, succumb to drug and alcohol abuse, though I think this is rarely the case—instead, drug and alcohol abuse is almost always a sign of Big Three strength abnormality and/or dysfunction. In other words, I think in almost all cases people self-medicate when their quality of life is lower than normal—in that they exhibit expanded dysthymia, described in the next chapter—and the drug or alcohol produces a significant improvement in quality of life. Therefore, a large fraction of drug and alcohol addicts would benefit from The Adjustment. The most common Big Three profile among drug and alcohol abusers is probably weak ser and/or strong nore.

Drug and alcohol abuse is also very common in overtly mentally ill individuals, such as those with unipolar depression, bipolar disorder, or anxiety disorders. Weak dop—and strong dop, as in mania and hypomania—has been strongly associated with addictive behavior.

Personality Disorders

The personality disorders include a broad range of psychiatric illnesses in which the individual probably experiences the world in a deviant manner and also exhibits various types of deviant behavior. These disorders may in part involve hardwired circuits that aren't affected by Big Three adjustments—this is the conventional wisdom, but I don't believe it's correct. Instead, I think the personality disorders are actually caused by genetically weak ser (and/or strong nore) interacting with hardwired circuits. So I think they can be treated somewhat by Big Three drugs, and early intervention may be preferable if there really is a developmental component to these disorders.

Personality disorders caused by weak ser (and possibly strong nore): paranoid, schizoid, schizotypal, antisocial, borderline, avoidant, dependent, and obsessive-compulsive. Those caused by strong nore (and possibly weak ser): histrionic and narcissistic. These latter two disorders may be related to Cloninger's strong nore reward dependence trait, discussed in Chapter 12.

Autism

The current theory hypothesizes that autism is caused by developmentally weak ser *and* weak nore, partly because autism is characterized by language delays and social awkwardness—essentially anti-dominant characteristics (where strong ser or nore produce dominance; see Chapter 13). If weak ser and weak nore are responsible for language acquisition difficulties in autism, maybe people with strong ser or nore have superior linguistic skills. Whether autism can be treated by strengthening ser and nore during postnatal (i.e., after birth) development, and whether it can be treated later in life by the same means, is unclear. SRIs given after development have shown some efficacy. A possible experiment: give autistic individuals 1) an SRI only, 2) an NRI only, 3) both an SRI and an NRI. Another experiment (that will probably never be done): give one autistic identical twin ser and/or nore strengthening drugs during development, take the

drugs away in adulthood, and then compare him with his never medicated twin. The bottom line is that autistic traits—such as low tolerance of stress; preservation of routine at all cost; that the illness may be precipitated by stressors; sensory sensitivity (though sometimes reduced sensitivity); paying attention to irrelevant details of objects; ADHD; depression; aggression; and sleep problems—all point to weak ser and possibly weak nore.

Impulse Control Disorders

These disorders may be caused by Big Three abnormalities interacting with hardwired circuits, and therefore are partially treatable with Big Three drugs. Inability to control anger may have two components: an intense feeling of anger itself, and the inability to prevent reaction to this feeling. As with drug and alcohol abuse, these disorders may be related to overt mental illnesses, such as ADHD (hypofrontality) and bipolar disorder (hypomania or mania). Weak ser and/or strong nore, accompanied by either weak or strong dop, may be the principal Big Three abnormalities.

Eating Disorders

I think these disorders are almost always accompanied by Big Three abnormalities, especially weak ser and/or strong nore. If self-esteem is partly encoded by strength of ser (see Chapter 7), then weak ser causing low self-esteem may play a critical role. Moreover, perhaps there is sometimes a relationship between weak ser and perceiving oneself as physically unattractive. As in drug and alcohol abuse, weak dop stimulus seeking may also play a role.

The eating disorders often coexist with other mental illnesses such as bipolar disorder, consistent with the hypothesis that ser tends to be weak and nore tends to be strong in both eating disorders and bipolar disorder.

Self-injurious behavior may also be characterized by weak ser and/or strong nore, and should be responsive to The Adjustment.